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# Third CECOG consensus on the systemic treatment of non-small-cell lung cancer

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The current third consensus on the systemic treatment of non-small-cell lung cancer (NSCLC) builds upon and updates similar publications on the subject by the Central European Cooperative Oncology Group (CECOG), which has published such consensus statements in the years 2002 and 2005 (Zielinski CC, Beinert T, Crawford J et al. Consensus on medical treatment of non-small-cell lung cancer—update 2004. Lung Cancer 2005; 50: 129–137). The principle of all CECOG consensus is such that evidence-based recommendations for state-of-the-art treatment are given upon which all participants and authors of the manuscript have to agree (Beslija S, Bonneterre J, Burstein HJ et al. Third consensus on medical treatment of metastatic breast cancer. Ann Oncol 2009; 20 (11): 1771–1785). This is of particular importance in diseases in which treatment options depend on very particular clinical and biologic variables (Zielinski CC, Beinert T, Crawford J et al. Consensus on medical treatment of non-small-cell lung cancer—update 2004. Lung Cancer 2005; 50: 129–137; Beslija S, Bonneterre J, Burstein HJ et al. Third consensus on medical treatment of metastatic breast cancer. Ann Oncol 2009; 20 (11): 1771–1785). Since the publication of the last CECOG consensus on the medical treatment of NSCLC, a series of diagnostic tools for the characterization of biomarkers for personalized therapy for NSCLC as well as therapeutic options including adjuvant treatment, targeted therapy, and maintenance treatment have emerged and strongly influenced the field. Thus, the present third consensus was generated that not only readdresses previous disease-related issues but also expands toward recent developments in the management of NSCLC. It is the aim of the present consensus to summarize minimal quality-oriented requirements for individual patients with NSCLC in its various stages based upon levels of evidence in the light of a rapidly expanding array of individual therapeutic options.

**Key words:** CECOG, chemotherapy, NSCLC, targeted therapy

## introduction

Lung cancer is one of the most frequently occurring malignancies in the world and represents the leading cause of cancer-related deaths in Western countries. Non-small-cell lung cancer (NSCLC) accounts for ~80% of all lung cancer cases. In 2006, lung cancer was in incidence the third most common cancer in Europe amounting to 386 300 cases and 12.1% of all incident cases [1]. In the same year and geographic area, lung cancer was the most frequent reason for death caused by a malignancy [1]. Age-standardized incidence rates per 100 000 were 75.3 in men and 18.3 in women, whereas the corresponding mortality rates were 64.8 in men and 15.1 in women [1]. Smoking has been unequivocally and very strongly

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shown to be tightly associated with disease occurrence representing the causative factor for ~90% of all lung cancers [2]. Environmental tobacco smoke is a scientifically documented concern and results in an increased risk for the development of lung cancer [2].

Systemic therapy (chemotherapy and targeted therapy) constitutes an essential element of multimodality therapy of NSCLC. In early NSCLC, >80% of recurrences occur within 2 years from the time of radical surgery. However, >70% of patients have locally advanced or metastatic disease already at presentation and thus require systemic treatment.

## method of consensus formation

### panel composition

The Central European Cooperative Oncology Group (CECOG) has invited an expert panel consisting of NSCLC experts from Europe and the United States to generate an evidence-based consensus on all aspects of the systemic treatment of NSCLC thus generating recommendations on how to optimize individual treatment administered to individual patients.

### literature review and analysis

In analogy to methods used for other CECOG consensus statements [2–4], electronic and manual searches including Medline and abstracts published in the proceedings of the most relevant topic-oriented international meetings including conferences of the American Society of Clinical Oncology, the European Conference of Clinical Oncology, the European Society of Medical Oncology and the World Conference of Lung Cancer were used for publication identification. For evidence-based clinical recommendations, publications from peer-reviewed journals or abstracts of randomized clinical phase III trials and meta-analyses on the systemic treatment of NSCLC were selected for discussion and subsequent inclusion in the manuscript. For the inclusion of manuscripts and the acknowledgment of the results of phase III clinical trials, a significant gain in treatment efficacy [prolongation of overall survival (OS) or progression-free survival (PFS)] had to be reported.

Levels of Evidence [I–V] and Grades of Recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets following concluding remarks summarizing each chapter.

### method of consensus formation

Subgroups of three to four panel participants were coordinated by one of its members. Each subgroup reviewed publications addressing particular aspects relating to the medical management of NSCLC including the following: (i) adjuvant and neoadjuvant (induction) chemotherapy, (ii) systemic therapy for advanced disease, (iii) supportive care and (iv) molecular markers.

Each subgroup reviewed and summarized data available until December 2009 relevant to these topics. Each subgroup presented a consensus proposal in writing. After extensive discussion among panelists via e-mail and after a 1-day meeting on 22 January 2010 in Vienna, Austria, a consensus was generated that represents a text upon which all panelists have agreed. Subsequently, final text editing was completed by all authors, circulated repeatedly between panelists by e-mail and, finally, accepted by all.

## adjuvant and neoadjuvant chemotherapy

### adjuvant chemotherapy

Despite of surgery and complete surgical resection of NSCLC, up to ~60% of patients experience recurrence of disease [5–7]. Thus, adjuvant chemotherapy in these patients with completely resected NSCLC has been proposed based on the assumption that distant micrometastases present at the time of diagnosis constitute the reason for recurrence of NSCLC in a considerable proportion of patients. Several adjuvant chemotherapy trials have been carried out [8–12]. A meta-analysis of five cisplatin-based trials revealed an increase of the 5-year survival rate following adjuvant chemotherapy by 5.3% [13].

Adjuvant cisplatin-based doublet chemotherapy (three to four cycles) should be offered to patients with stage II and III disease and may be considered for selected patients based on tumor size with stage IB disease with adequate postoperative recovery, absence of clinically relevant comorbidity and good performance status (PS) within 2 months after surgery. Cisplatin should be preferred over carboplatin and combined with a third-generation cytotoxic drug, preferentially vinorelbine. A subgroup analysis of the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analyses [14] revealed a superior survival of the combination of cisplatin with vinorelbine, as compared with other cisplatin-based doublets [overall test of interaction $P = 0.04$; hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.70–0.91, $P < 0.001$ for LACE-vinorelbine and HR 0.95, 95% CI 0.86–1.05, $P = 0.33$ for LACE-other]. Importantly, patients randomly assigned to receive cisplatin–vinorelbine constituted the largest (41%) and the most homogeneous subgroup in terms of cisplatin dose. Although grade 3–4 toxicity was more common, the LACE preplanned subanalysis confirmed a survival benefit in NSCLC of stages II and III in patients receiving cisplatin with vinorelbine [14].

### neoadjuvant (induction) chemotherapy

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*conclusions.*

1. Surgery remains the mainstay of treatment of early NSCLC [Level of Evidence: I,A].
2. Adjuvant chemotherapy after complete tumor resection should be offered to patients with stage II and III [I,A] disease and may be considered for selected patients based on tumor size with stage IB disease. Chemotherapy should consist of cisplatin plus a third-generation cytotoxic drug, preferentially vinorelbine [I,B].
3. Neoadjuvant (induction) chemotherapy may be considered in stage III disease [II,B].

## systemic therapy for advanced disease

### first-line therapy

*platinum-based chemotherapy.* Chemotherapy improves survival and quality of life (QoL) and palliates tumor-related symptoms in patients with good PS [15]. The evidence of efficacy is best documented for platinum-based regimens. Therefore, platinum-based doublet combinations are recommended in patients with PS of zero or one.

According to a meta-analysis, cisplatin is preferred over carboplatin under consideration of different toxic effects of the two drugs [16]. Cisplatinum-based treatment should be delivered in combination with preferentially third-generation cytotoxic drugs [16]. There is no evidence that a cisplatin dose

of >75–80 mg/m$^2$ delivered every 3–4 weeks might ameliorate treatment outcome [17]. First-line cytotoxic chemotherapy should be administered for four to six cycles but should be stopped at disease progression. Non-platinum-based therapy can be considered in patients who have contraindications to platinum treatment and in unfit elderly patients.

A randomized phase III trial has indicated that pemetrexed exerts optimal activity in nonsquamous NSCLC [18]: the pivotal trial [18] was a noninferiority study including 1700 chemonaive patients with stage IIIB–IV NSCLC and a PS of zero or one. Patients were randomly assigned to receive cisplatin in combination with either gemcitabine or pemetrexed for up to six cycles. OS was similar in both arms. However, when analyzed by histology, patients with adenocarcinoma and large-cell carcinoma showed significantly superior OS with cisplatin–pemetrexed, as compared with cisplatin–gemcitabine. The inverse was true for patients with squamous cell carcinoma. Based on these results, cisplatin–pemetrexed was approved by European Medicines Agency (EMA) in patients with nonsquamous NSCLC.

Selection of first-line therapy may thus be based on clinical criteria, histological subtype [18] and epidermal growth factor receptor (EGFR) mutation status [21].

*conclusions*:

1. Platin-based doublets containing a third-generation cytotoxic drug is the treatment of choice in patients with advanced NSCLC, unless platinum is contraindicated [I,A].
2. Cisplatin might be preferred in patients with good PS.
3. Nonsquamous histology is a prerequisite for pemetrexed efficacy [I,B].
4. Cisplatin doses of <75–80 mg/m$^2$ every 3–4 weeks are recommended [I,B].
5. Chemotherapy should be given for four to six cycles but stopped at disease progression [II,B].

*targeted therapies bevacizumab*: Two randomized studies indicated the efficacy of the antiangiogenesis compound bevacizumab [19, 20]. The design of the pivotal intergroup trial foresaw the continuation of bevacizumab after the termination of chemotherapy until disease progression or unacceptable toxicity [20]. This phase III trial that randomly analyzed treatment efficacy by the addition of bevacizumab 15 mg/kg every 3 weeks to paclitaxel and carboplatin found a statistically significant increase of OS as well as of PFS in the bevacizumab-containing treatment arm [20]. Another phase III trial (AVAIL: Avastin in Lung) on the efficacy of bevacizumab (7.5 or 15 mg/kg every 3 weeks) combined with gemcitabine and cisplatin confirmed the PFS benefit in patients randomly assigned to receive bevacizumab plus chemotherapy but did not confirm an improvement of OS [19].

Based on presently available data, the use of bevacizumab is not indicated in patients with squamous cell histology in whom an increased rate of hemorrhages was observed [23].

*conclusions.* The addition of bevacizumab to first-line chemotherapy (either carboplatin–paclitaxel or cisplatin–gemcitabine) of advanced nonsquamous NSCLC provides benefit in patients with good PS and age < 70 [I,B]. The dose of bevacizumab may be either 7.5 or 15 mg/kg every 3 weeks depending on the chemotherapeutic backbone.

*cetuximab:* In a large pivotal trial (FLEX: First-Line Erbitux in Lung Cancer) NSCLC patients with EGFR-positive advanced NSCLC (assessed by immunohistochemistry) were randomly assigned to receive cisplatin plus vinorelbine with or without cetuximab. Cetuximab was given weekly until progression of disease [22]. Patients assigned to the cetuximab group demonstrated a modestly longer median OS [11.3 versus 10.1 months; HR 0.871 (95% CI 0.762–0.996); $P = 0.044$] and a higher response rate (RR), whereas there was no difference in PFS. Most common cetuximab-related side-effects were acne-like skin rash, diarrhea and infusion-related reactions. The cetuximab-induced benefit was independent of histology subtype, gender or smoking status. Similarly, *K-RAS* mutation status was not predictive for cetuximab efficacy, whereas early acne-like rash of any grade was associated with better outcome [24, 25]. In another phase III study (BMS-099), the addition of cetuximab to carboplatin plus a taxane failed to improve the primary end point of PFS [26].

In a recent meta-analysis based on individual data of 2018 patients from four randomized phase II or III trials, the median OS in patients who received cetuximab in addition to chemotherapy was 10.3 months, as compared with 9.4 months in the chemotherapy-only arm [HR 0.878 (95% CI 0.795–0.969); $P = 0.01$] corresponding to an absolute benefit of 4.8% at 1 year [27]. PFS was also more favorable for chemotherapy plus cetuximab [HR 0.89 (95% CI 0.81–0.99); $P = 0.03$].

*conclusion*s. Despite these results, the US Food and Drug Administration label for cetuximab does not yet include NSCLC, and the EMA did not grant its use in this indication owing to modest benefits and associated toxicity. Nevertheless, addition of cetuximab to a platinum-based chemotherapy regimen is a treatment option in advanced NSCLC [I,B].

*EGFR tyrosine kinase inhibitors*: Four trials examined the efficacy of EGFR tyrosine kinase inhibitors (TKIs) erlotinib or gefitinib in combination with cytotoxic chemotherapy doublets in the first-line setting [28–31]. All four trials found no improvement in OS, PFS or RR with the addition of an EGFR TKI to chemotherapy. Therefore, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line treatment in unselected patients.

In contrast, the first-line use of gefitinib as single agent has shown efficacy in patients with EGFR-activating mutations in a large randomized phase III trial (IPASS: Iressa Pan-Asia Study) comparing gefitinib given until disease progression with chemotherapy consisting of paclitaxel plus carboplatin as first-line treatment in a population specific to East Asia [21]. The primary end point of PFS was significantly longer with gefitinib. OS, a secondary end point, did not differ. Hematotoxicity, alopecia, neuropathy and nausea were more pronounced in the chemotherapy arm, whereas diarrhea and skin toxicity were more frequent in the gefitinib arm. Patients with EGFR-activating mutations experienced a better outcome with gefitinib,

whereas patients without mutations had more benefit from chemotherapy.

*conclusions*.

1 It is strongly recommended to test for EGFR-activating mutations [I,A].
2 In the absence of EGFR-activating mutations, chemotherapy remains the treatment of choice [I,A].
3 In patients with EGFR-activating mutations, treatment with gefitinib is the preferred treatment option [I,A].

*Eastern Cooperative Oncology Group PS of two*. Available data support the use of single-agent chemotherapy in patients with Eastern Cooperative Oncology Group PS of two. However, data are still insufficient to make a recommendation for or against using a combination of two cytotoxic drugs for patients with PS of two [15,32–35].

*treatment in the elderly*. Full version is available at *Annals of Oncology* online.

*conclusions*: Single-agent therapy remains a reasonable option for unfit elderly patients [I,B] [26, 36 37], although clinical evidence does not support selection of a specific first-line chemotherapy drug or combination based on age alone. However, the need for enhanced supportive care should be emphasized in this patient population.

### maintenance therapy

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*conclusions*. The administration of pemetrexed in nonprogressing patients with nonsquamous NSCLC immediately after first-line platinum-based chemotherapy [I,B] and erlotinib in patients with NSCLC who experienced stable disease by first-line chemotherapy [I,B] constitute registered options.

### second-line systemic therapy

In patients treated with first-line chemotherapy for advanced NSCLC, disease progression usually occurs within 3–5 months. Second-line therapy at progression palliates tumor-related symptoms and improves survival [38]. The benefit of second-line therapy is more likely in patients who have responded to first-line chemotherapy and who have a good PS [39].

Efficacy of second-line chemotherapy was first demonstrated in a phase III trial of docetaxel against best supportive care. This trial showed significant benefit for OS and QoL achieved by the administration of docetaxel despite the risk of toxicity [40].

*chemotherapy.* Docetaxel had initially been established as a standard in NSCLC [40, 41]. However, pemetrexed showed similar efficacy but a more favorable toxicity profile, as compared with docetaxel in a study originally designed to prove noninferiority [42]. In a *post hoc* analysis, the benefit achieved by pemetrexed was found to occur in patients with nonsquamous tumors and this subsequently resulting in a limitation change of the pemetrexed label.

*targeted agents. epidermal growth factor receptor tyrosine kinase inhibitors*: Erlotinib and gefitinib were investigated for efficacy in pretreated patients [44, 45]. A phase III study comparing erlotinib with placebo in stage IIIB or IV NSCLC patients who had received one to two prior combination chemotherapy regimens and were not candidates for further cytotoxic treatment demonstrated significant, albeit moderate, clinical benefit of erlotinib {median OS of 6.7 and 4.7 months for erlotinib and placebo, respectively [HR 0.70 (0.58–0.85); $P < 0.001$]} [44]. Patients treated with erlotinib had also improvements in pain, cough and dyspnea. The most common side-effect of erlotinib was acneiform rash and diarrhea (75% and 55%, respectively) although grades 3–4 toxicity occurred in >10% of patients. High EGFR gene copy number by FISH was the strongest predictive marker for clinical benefit from erlotinib [46].

A similarly designed phase III trial (ISEL: Iressa Survival Evaluation in Lung Cancer) evaluating gefitinib versus placebo in advanced NSCLC patients in whom one or two prior chemotherapy regimens failed did not reach significant OS superiority [HR 0.89 (95% CI 0.77–1.02); $P = 0.087$] [45]. However, in preplanned subgroup analyses, OS was significantly longer with gefitinib in never smokers and patients of Asian ethnicity. Similarly to the BR 21 study, the clinical benefit obtained from gefitinib was associated with high EGFR gene copy number [47]. In a large noninferiority randomized study (INTEREST: Iressa NSCLC Trial evaluating response and Survival against Taxotere comparing gefitinib versus docetaxel in previously treated advanced NSCLC patients, gefitinib was equivalent to chemotherapy for survival and superior for the secondary end point QoL [43].

*conclusions.*

1 The data from randomized trials on second-line therapy are sufficient to recommend either a cytotoxic agent (docetaxel for squamous NSCLC [II,B] or pemetrexed for nonsquamous NSCLC [II,B]) or the EGFR TKI erlotinib [I,B].
2 An EGFR TKI should be strongly considered in patients with EGFR-activating mutations in their tumors who have not received it as first-line treatment [II,B]. Sequencing of chemotherapy after EGFR TKIs has not been defined and remains an important open issue.

## supportive care

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## molecular markers

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### targeted treatment options

*EGFR-related biomarkers for prognosis.* A meta-analysis of several studies failed to show a consistent correlation between EGFR expression levels and survival [49]. Most studies have shown no prognostic effect of EGFR expression or a slight detrimental effect. The results for activating EGFR mutations are strikingly different. Nearly all studies reported that patients with these mutations have

**Table 1.** Author disclosures

| | Speakers honoraria | Advisory board |
|---|---|---|
| VG | Research grants: Glaxo, Pfizer, Merck Serono, Amgen, Novartis | Glaxo Smith Kline (GSK), Novartis, Pfizer, Sanofi Aventis |
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| JJ | | Bristol-Myers Squibb, GSK |
| MK | Merck Serono, Roche, Pierre Fabre, Eli Lilly | |
| ChM | Roche, Merck, Eli Lilly, AstraZeneca | Abraxis, Agennix, AstraZeneca, Amgen, Boehringer Ingelheim, Merck, Eli Lilly, Roche |
| JLP | Roche, Eli Lilly, Celgen, Böhringer Ingelheim, Merck Serono, GSK | Amgen |
| RS | Roche, Eli Lilly | Roche, Bristol-Myers Squibb, GSK, Eli Lilly, AstraZeneca |
| NT | Honoraria for speaker, chairing and advisory board over the last 2 years from Roche, Lilly, Merck Serono, Bristol-Myers Squibb, GSK, AstraZeneca, Pfizer, Bohringer Ingelheim, Amgen, Bayer | |
| JV | | Eli Lilly: chair Respiratory Oncology; Amgen: chair Supportive Cancer Care; Roche chair in Molecular Targeted Therapy |
| CZ | Roche | Roche, Bristol-Myers Squibb, Pfizer, GSK |
| SZ-M | Eli Lilly, Sanofi Aventis, Merck | AstraZeneca |
| MF | AstraZeneca, Eli Lilly, Glaxo Smith Kline, Merck | AstraZeneca |
| TB | Eli Lilly, Roche | |

a better outcome compared with those without these mutations, irrespective of tumor stage and treatment [48–51].

*prediction of outcome of EGFR-targeted therapy*: About 10% of NSCLC patients in a Western population and 30%–50% in East Asia have EGFR-activating mutations. A randomized phase II study showed that in patients with EGFR-activating mutations, the median PFS was 18.2 months with erlotinib compared with 4.9 months with the alteration of chemotherapy and erlotinib. In contrast, the chemotherapy arm had a better median PFS in patients without an EGFR-activating mutation [52]. There is no evidence that EGFR-activating mutations predict for superior outcome following cetuximab therapy [25].

While K-RAS mutation has been demonstrated to be a negative predictor in EGFR inhibition in patients with metastatic colorectal cancer, its role in NSCLC patients is still under debate.

*EML4-ALK fusion.* The fusion gene EML4-Anaplastic Lymphoma Kinase (ALK) was first reported in NSCLC only a few years ago [53]. A clinical dose-escalation phase I study with an oral MET and ALK inhibitor PF-02341066 showed for NSCLC patients with tumors harboring an activating ALK gene fusion an objective RR of 64% and a disease control rate of 90% [54]. Although the ALK fusion either with EML4 or with other fusion partners is relatively infrequent in NSCLC (4%–5%), there still is a substantial number of patients who might have a significant clinical benefit from this well-tolerated therapy [55].

*conclusions*:

1. EGFR mutations predict a better response to EGFR TKIs (i.e. gefitinib) compared with chemotherapy as first-line therapy in advanced NSCLC. Thus, EGFR mutation testing should be encouraged before treatment decision [I,A].
2. K-RAS mutation predicts a low response to EGFR TKIs, but a significant association with survival was demonstrated for neither EGFR TKI nor EGFR-directed antibody therapy. Testing should not be recommended as a basis for treatment decisions in routine practice.
3. Patients with EML4-ALK fusion tumors benefit from specific targeted therapy against EML4-ALK fusion. The role of routinely carried out EML4-ALK fusion testing for clinical practice is awaiting the results from ongoing clinical trials.

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## disclosures

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